REPROGRAMMING UROKINASE INTO AN ANTIBODY-RECRUITING ANTICANCER AGENT

[0001] This application claims the benefit of priority of U.S. provisional application 61/558,811, filed Nov. 11, 2011, entitled "ARM-U: Reprogramming urokinase to serve as an antibody-recruiting anticancer agent", the entire contents of which is incorporated by reference.

[0002] This invention was made with government support under 1DP20D002913-01 awarded by the National Institute of Health. The government has certain rights in the invention.

FIELD OF THE INVENTION

[0003] The present invention relates to chimeric (including bifunctional) compounds, compositions comprising those compounds and methods of treating cancer in a patient or subject, especially including metastatic cancer where cancer cells exhibit ovrexpression (heightened expression) of cell surface urokinase-type plasminogen activator receptor (urokinase receptor) compared to normal (non-cancerous) cells. The compounds preferably covalently bind to the urokinase-type plasminogen activator (uPA) on the surface of a cancer cell, including a metastatic cancer cell, and consequently recruit native antibodies of the patient or subject where the antibodies can selectively degrade and/or deactivate targeted cancer cells through antibody-dependent cellular phagocytosis and antibody-dependent cellular cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC) against a large number and variety of cancers, thus providing cancer cell death and an inhibition of growth, elaboration and/or metastasis of the cancer, including remission and cure of the patient's cancer.

BACKGROUND OF THE INVENTION

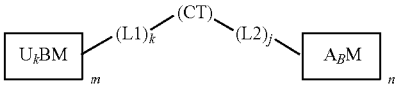
[0004] Cancer is currently the second leading cause of death in the United States, having claimed over half a million American lives in 2010.[i] In general, metastatic cancers are particularly difficult to treat and are associated with higher levels of morbidity and mortality compared to localized tumors.[ii,iii] For example, while the five-year survival rate of patients with localized melanoma is >95%, this survival rate drops to 15-30% for patients whose disease has metastasized to distant locations.[i] Since American men and women have a 38-44% chance, respectively, of developing invasive cancers during their lifetimes,[i] novel strategies for treating advanced-stage invasive cancers have the potential to provide profound therapeutic impact.

[0005] Tumor metastasis begins with cancer cells invading surrounding tissues. This process is frequently accelerated by cell-surface proteases, including uPA,[iv,v,vi] which are capable of breaking down extracellular matrix proteins and activating migration-inducing signal transduction cascades.[vii,viii] uPA binds uPAR on the extracellular surface of many cancer cells, including those of the breast, colon, stomach, and bladder.[ix,x] Extensive evidence suggests that the levels of uPA and uPAR expression are substantially higher on invasive, malignant cancer cells than on either healthy tissues or benign tumors.[v,ix,xi,xii,xiii,xiv] Indeed, in clinical settings, high levels of uPA and uPAR are used as diagnostic markers for metastatic potential and poor clinical outcome in numerous malignancies.[iv,v,x,xv,xvi,xvii,xviii,xix,xx] For these reasons uPA and uPAR have emerged as promising therapeutic targets.[ix,xxi] Data has shown that inhibitors and cytotoxic fusion proteins that target the uPAuPAR system can both reduce the invasive potential of cancer cells[xxii,xxiii] and reduce tumor volumes in animal models[xxiv,xxv,xxvi] without significantly damaging healthy tissue.[xxvi]

[0006] The growing field of synthetic immunology[xxvii] aims to develop novel synthetic materials capable of modulating the human immune system. One emerging concept in this area is to use bifunctional molecules to direct normal immune responses to attack cancer cells that are not sufficiently recognized and suppressed by the immune system on its own.[xxviii,xxix,xxx,xxxi,xxxii] We report here a novel application of this strategy to direct endogenous immunological effector mechanisms to act against uPAR-expressing human cancer cells (FIG. **1**). We have designed and synthesized two small molecules that can convert uPA into catalytically inactive, bifunctional constructs (ARM-Us) that are capable of both recruiting antibodies and directing antibody-dependent immune responses against uPAR-expressing cancer cells. These small molecules quantitatively inhibit uPA's enzymatic activity by covalently binding to its active site, and this covalent modification simultaneously appends either a 2,4-dinitrophenyl (DNP) moiety or a fluorescein label. The DNP antigen is of particular interest for therapeutic application because anti-DNP antibodies have been found endogenously in the plasma of most humans.[xxxiii] Here we demonstrate that ARM-U can bind with high affinity to uPAR-expressing cancer cells, recruit antibodies to these cells, and induce phagocytosis and cytotoxicity in an antibody-dependent immune-mediated fashion. The technology reported herein represents a novel strategy to target uPAR-expressing cancers and has significant potential to impact the treatment of a variety of deadly malignancies.

BRIEF DESCRIPTION OF THE INVENTION

[0007] The present invention is directed to a compound (also referred to as a precursor compound or ARM-U precursor compound) according to the formula:



Where

[0008]

is a moiety which covalently or non-covalently (preferably covalently) binds to an active site of urokinase-type plasminogen activator (uPA) on the surface of cancer cells of a patient or subject;